

In re Application of: Sawynok et al.
Application No.: 09/700,625
Filing Date: February 1, 2001
Page 5 of 14

PATENT
Attorney Docket No.: DALHO1290-1
(028614-1102)

Remarks

The present invention provides compositions containing second or third generation antidepressants, formulated for local or topical administration. Invention compositions have been shown to produce local analgesia in subjects having a site of local discomfort. Invention formulations possess the advantage of providing a higher and more efficacious concentration of antidepressant to the region of the sensory nerve terminal than is achievable with systemic administration of the same antidepressant. In addition, invention compositions for local or topical administration greatly reduce the side effects that may result from systemic administration of antidepressants.

Claims 26, 37-44, 49-53, 72 and 73 were pending prior to the present communication. By this response, claims 26 and 37 have been amended, and new claims 74-83 have been added to define Applicants' invention with greater particularity. Specifically, the tricyclic antidepressants desipramine, nortriptyline and protriptyline, and the selective serotonin reuptake inhibitor (SSRI) fluoxetine, have been removed from claim 26, because they were inadvertently included as second or third generation antidepressants. These amendments and new claims add no new matter as they are fully supported by the specification and original claims. For the Examiner's convenience, a marked up version of the changes made to the claims is provided herewith, labeled as APPENDIX A.

Accordingly, claims 26, 37-44, 49-53 and 72-83 are currently pending. For the Examiner's convenience a clean copy of all pending claims is provided herewith as APPENDIX B.

The rejection of claims 26, 42-44, 49, 50 and 72 under 35 U.S.C. § 102(b), as allegedly being anticipated by Bernstein *et al.*, U.S. Patent No. 4,603,131 (hereinafter " '131' ") is respectfully traversed. Applicants' invention, as defined, for example, by claim 26, distinguishes over '131 by containing a second or third generation antidepressant. '131 does not disclose any

In re Application of: Sawynok et al.
Application No.: 09/700,625
Filing Date: February 1, 2001
Page 6 of 14

PATENT
Attorney Docket No.: DALHO1290-1
(028614-1102)

compositions containing a second or third generation antidepressant. In contrast, '131 only discloses compositions containing the tricyclic antidepressants doxepin, amitriptyline, imipramine, nortriptyline, protriptyline and desipramine. Indeed, '131 itself acknowledges that these are all tricyclic antidepressants (see, e.g., abstract and claim 1).

To the extent that there may be confusion based on the use of the terms "secondary amines" and "tertiary amines" in '131, Applicants respectfully submit that these terms merely refer to different types of tricyclic antidepressants, and are completely distinct from second or third generation antidepressants. Applicants enclose an excerpt from the text "Basic and Clinical Pharmacology", which shows the classification of all of these compounds as tricyclic antidepressants. Therefore, '131 does not disclose second or third generation antidepressant compositions as required by the present claims. Accordingly, reconsideration and withdrawal of this rejection of claims 26, 42-44, 49, 50 and 72 are respectfully requested.

In addition, it is respectfully submitted that this rejection does not apply to any of the new claims presented herein, i.e., claims 74-83. New claims 74-83 are also all directed to compositions of second or third generation antidepressants, which are not disclosed by '131.

The rejection of claims 26, 42, 44, 49, 50 and 72 under 35 U.S.C. § 102(b), as allegedly being anticipated by Quan *et al.*, U.S. Patent No. 5,601,839 (hereinafter "'839") is respectfully traversed. Applicants' invention, as defined, for example, by claim 26, distinguishes over '839 by containing a second or third generation antidepressant. '839 does not disclose any compositions containing a second or third generation antidepressant. In contrast, '839 only discloses three antidepressants amongst the list of basic drugs contemplated therein (see '839 at column 3, lines 55-60); the tricyclic antidepressants imipramine and desipramine, and fluoxetine, which is classified as SSRI (see text excerpt). In addition, as amended, fluoxetine has also been removed from claim 26 as noted above. Therefore, '839 does not disclose second or third generation antidepressant compositions as required by the present claims. Accordingly,

In re Application of: Sawynok et al.
Application No.: 09/700,625
Filing Date: February 1, 2001
Page 7 of 14

PATENT
Attorney Docket No.: DALHO1290-1
(028614-1102)

reconsideration and withdrawal of this rejection of claims 26, 42, 44, 49, 50 and 72 are respectfully requested.

In addition, it is respectfully submitted that this rejection does not apply to any of the new claims presented herein, *i.e.*, claims 74-83. New claims 74-83 are also all directed to compositions of second or third generation antidepressants, which are not disclosed by '839.

The rejection of claims 26, 42, 44, 49, 50, 52, 53 and 72 under 35 U.S.C. § 103(a) as allegedly being unpatentable over '839, in view of Kitchell *et al.*, U.S. Patent No. 5,486,362 (hereinafter "'362'"), is respectfully traversed. As noted above, '839 does not teach or suggest a composition comprising a second or third generation antidepressant.

Furthermore, '362 is unable to cure the deficiencies of '839, because it also does not teach or suggest compositions comprising a second or third generation antidepressant. In contrast, '362 only mentions the tricyclic antidepressant desipramine or the SSRI fluoxetine amongst the list of drug substitutes contemplated therein (see '362 at column 3, lines 1-30). Therefore, the cited references, either taken alone or in combination, do not teach or suggest a required element of the present composition, specifically, a second or third generation antidepressant. Accordingly, reconsideration and withdrawal of this rejection of claims 26, 42, 44, 49, 50, 52, 53 and 72 are respectfully requested.

In addition, it is respectfully submitted that this rejection does not apply to any of the new claims presented herein, *i.e.*, claims 74-83. New claims 74-83 are also all directed to compositions of second or third generation antidepressants, which are not disclosed by '839 or '362.

The rejection of claims 26, 37-43, 50, 51, 72 and 73 under 35 U.S.C. § 103(a) as allegedly being unpatentable over Gamble *et al.*, U.S. Patent No. 4,840,952 (hereinafter "'952'"), in view of Silvestrini *et al.*, U.S. Patent No. 4,154,832 (hereinafter "'832'"), is respectfully

In re Application of: Sawynok et al.
Application No.: 09/700,625
Filing Date: February 1, 2001
Page 8 of 14

PATENT
Attorney Docket No.: DALHO1290-1
(028614-1102)

traversed. Applicants' invention, as defined by independent claims 26 and 37, as amended (and claims 38-43, 50, 51, 72 and 73 dependent therefrom), distinguish over the applied art because these claims specifically exclude trazodone in a composition for local administration. In contrast, both '952 and '832 only disclose the use of a single compound, *i.e.*, trazodone, the very compound excluded by the subject claims. Accordingly, reconsideration and withdrawal of this rejection of claims 26, 37-43, 50, 51, 72 and 73 are respectfully requested.

In addition, it is respectfully submitted that this rejection does not apply to any of the new claims presented herein, *i.e.*, claims 74-83. Claims 74-76 and 79-81 specifically require a vehicle for topical administration, wherein the topical vehicle is a cream, a lotion, a gel, an ointment, a spray, a patch, a polymer stabilized crystal or an aerosol. Claims 77-78 and 82-83 also require a vehicle for topical administration, specifically a slow release delivery vehicle. Neither '952 nor '832 teach or suggest a composition comprising the specific vehicles required by the present claims for topical administration of a second or third generation antidepressant. Accordingly, this rejection does not apply to newly added claims 74-83.

Conclusion

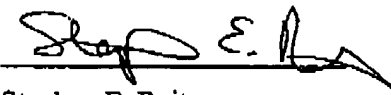
In view of the above amendments and remarks, reconsideration and favorable action on all claims are respectfully requested. In the event any matters remain to be resolved in view of this communication, the Examiner is encouraged to call the undersigned so that a prompt disposition of this application can be achieved.

Respectfully submitted,

Date: January 28, 2003

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Enclosures: **Appendices A and B**
Text excerpt (3 pages)


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In re Application of: Sawynok et al.
Application No.: 09/700,625
Filing Date: February 1, 2001
Page 9 of 14

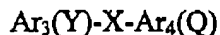
PATENT
Attorney Docket No.: DALHO1290-1
(028614-1102)

APPENDIX A – AMENDED CLAIMS
VERSION WITH MARKINGS TO SHOW CHANGES MADE

Claims 26 and 37 have been amended as follows:

26. (Thrice amended) A composition for local administration comprising a second or third generation antidepressant, and a vehicle suitable for local administration, wherein the second or third generation antidepressant is selected from the group consisting of amoxapine, [~~desipramine,~~] maprotiline, [~~nortriptyline, protriptyline, trazodone,~~] bupropion, mirtazapine, venlafaxine, nefazodone[, and reboxetine[, ~~and fluoxetine~~].

37. (Twice amended) A composition for local administration comprising a second or third generation antidepressant other than trazodone, and a vehicle suitable for local administration, wherein the second or third generation antidepressant has a structure:



wherein:

Ar₃ is a substituted N-containing heterocyclic ring,

Y is either an aryl group fused to the heterocyclic ring, or one or two substituents selected from the group consisting of alkyl, alkyloxy, arylalkyl, arylalkyloxy, aryl, heteroaryl substituents, and combinations thereof comprising a total of about 4 to 8 carbons attached to Ar₃,

X is an alkyl group comprising 2 to 5 carbon atoms linking Ar₃ and Ar₄,

Ar₄ is a piperazine attached to X by a first nitrogen atom of Ar₄, and

Q is a benzene ring optionally substituted with a biocompatible halogen and attached to Ar₄ at a second nitrogen atom of Ar₄.

New claims 74-83 have been added.

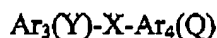
In re Application of: Sawynok et al.
Application No.: 09/700,625
Filing Date: February 1, 2001
Page 10 of 14

PATENT
Attorney Docket No.: DALHO1290-1
(028614-1102)

APPENDIX B – COMPLETE SET OF PENDING CLAIMS

26. (Thrice amended) A composition for local administration comprising a second or third generation antidepressant, and a vehicle suitable for local administration, wherein the second or third generation antidepressant is selected from the group consisting of amoxapine, maprotiline, bupropion, mirtazapine, venlafaxine, nefazodone and reboxetine.

37. (Twice amended) A composition for local administration comprising a second or third generation antidepressant other than trazodone, and a vehicle suitable for local administration, wherein the second or third generation antidepressant has a structure:



wherein:

Ar₃ is a substituted N-containing heterocyclic ring,

Y is either an aryl group fused to the heterocyclic ring, or one or two substituents selected from the group consisting of alkyl, alkyloxy, arylalkyl, arylalkyloxy, aryl, heteroaryl substituents, and combinations thereof comprising a total of about 4 to 8 carbons attached to Ar₃,

X is an alkyl group comprising 2 to 5 carbon atoms linking Ar₃ and Ar₄,

Ar₄ is a piperazine attached to X by a first nitrogen atom of Ar₄, and

Q is a benzene ring optionally substituted with a biocompatible halogen and attached to Ar₄ at a second nitrogen atom of Ar₄.

38. (Reiterated) The composition according to claim 37 wherein the X is an alkyl group containing 3 carbons.

39. (Reiterated) The composition according to claim 37 wherein Ar₃ is a 1,2,4-triazole substituted at the 4 position with the arylalkyloxy substituent containing 6 to 8 carbon atoms.

40. (Reiterated) The composition according to claim 39 wherein the heteroarylalkyl substituent contains an oxygen atom.

In re Application of: Sawynok et al.
Application No.: 09/700,625
Filing Date: February 1, 2001
Page 11 of 14

PATENT
Attorney Docket No.: DALHO1290-1
(028614-1102)

41. (Reiterated) The composition according to claim 37 wherein the benzene ring is substituted with a halogen selected from the group consisting of chlorine, bromine, and fluorine.

42. (Previously amended) The composition of claim 26 further comprising an inert carrier.

43. (Previously amended) The composition of claim 42 wherein the inert carrier is selected from the group consisting of water, isopropyl alcohol, gaseous fluorocarbons, ethyl alcohol, polyvinyl pyrrolidone, propylene glycol, a fragrance, a gel-producing material, stearyl alcohol, stearic acid, spermaceti, sorbitan monooleate, methylcellulose, and suitable combinations of any two or more thereof.

44. (Reiterated) The composition according to claim 26 wherein the composition further comprises a penetration enhancing agent.

49. (Previously amended) The composition according to claim 26 in a formulation selected from the group consisting of a cream, a lotion, a gel, an ointment, a spray, a patch, a polymer stabilized crystal, and an aerosol.

50. (Reiterated) The composition of claim 26 further comprising a neutralizing agent.

51. (Reiterated) The composition of claim 26 wherein the composition is formulated for local injection.

52. (Reiterated) The composition according to claim 26 wherein the antidepressant is encapsulated in a slow release delivery vehicle.

53. (Previously amended) The composition according to claim 52 wherein the delivery vehicle is selected from the group consisting of a liposome, a microcapsule, and a polymer stabilized crystal.

In re Application of: Sawynok et al.
Application No.: 09/700,625
Filing Date: February 1, 2001
Page 12 of 14

PATENT
Attorney Docket No.: DALHO1290-1
(028614-1102)

72. (Reiterated) The composition according to claim 26, wherein the concentration of second or third generation antidepressant in said composition falls in the range of about 0.5 up to 10 wt %.

73. (Reiterated) The composition according to claim 37, wherein the concentration of second or third generation antidepressant in said composition falls in the range of about 0.5 up to 10 wt %.

74. (New) A composition for topical administration comprising:
a second or third generation antidepressant, and
a vehicle suitable for topical administration,
wherein the second or third generation antidepressant is selected from the group consisting of amoxapine, maprotiline, trazodone, bupropion, mirtazapine, venlafaxine, nefazodone, reboxetine, and fluoxetine, and
wherein said vehicle is selected from the group consisting of a cream, a lotion, a gel, an ointment, a spray, a patch, a polymer stabilized crystal, and an aerosol.

75. (New) The composition of claim 74, wherein the composition further comprises a penetration enhancing agent.

76. (New) The composition of claim 74, wherein the composition further comprises a neutralizing agent.

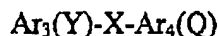
77. (New) A composition for topical administration comprising:
a second or third generation antidepressant, and
a vehicle suitable for topical administration,
wherein the second or third generation antidepressant is selected from the group consisting of amoxapine, maprotiline, trazodone, bupropion, mirtazapine, venlafaxine, nefazodone, reboxetine, and fluoxetine, and
wherein said vehicle is a slow release delivery vehicle.

In re Application of: Sawynok et al.
Application No.: 09/700,625
Filing Date: February 1, 2001
Page 13 of 14

PATENT
Attorney Docket No.: DALHO1290-1
(028614-1102)

78. (New) The composition of claim 77, wherein the slow release delivery vehicle is selected from the group consisting of a liposome, a microcapsule, and a polymer stabilized crystal.

79. (New) A composition for topical administration comprising a second or third generation antidepressant, and a vehicle suitable for topical administration, wherein the second or third generation antidepressant has a structure:



wherein:

Ar_3 is a substituted N-containing heterocyclic ring,

Y is either an aryl group fused to the heterocyclic ring, or one or two substituents selected from the group consisting of alkyl, alkyloxy, arylalkyl, arylalkyloxy, aryl, heteroaryl substituents, and combinations thereof comprising a total of about 4 to 8 carbons attached to Ar_3 ,

X is an alkyl group comprising 2 to 5 carbon atoms linking Ar_3 and Ar_4 ,

Ar_4 is a piperazine attached to X by a first nitrogen atom of Ar_4 , and

Q is a benzene ring optionally substituted with a biocompatible halogen and attached to Ar_4 at a second nitrogen atom of Ar_4 , and

wherein said vehicle is selected from the group consisting of a cream, a lotion, a gel, an ointment, a spray, a patch, a polymer stabilized crystal, and an aerosol.

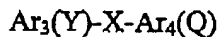
80. (New) The composition of claim 79, wherein the composition further comprises a penetration enhancing agent.

81. (New) The composition of claim 79, wherein the composition further comprises a neutralizing agent.

In re Application of: Sawynok et al.
Application No.: 09/700,625
Filing Date: February 1, 2001
Page 14 of 14

PATENT
Attorney Docket No.: DALHO1290-1
(028614-1102)

82. (New) A composition for topical administration comprising a second or third generation antidepressant, and a vehicle suitable for topical administration, wherein the second or third generation antidepressant has a structure:



wherein:

Ar_3 is a substituted N-containing heterocyclic ring,

Y is either an aryl group fused to the heterocyclic ring, or one or two substituents selected from the group consisting of alkyl, alkyloxy, arylalkyl, arylalkyloxy, aryl, heteroaryl substituents, and combinations thereof comprising a total of about 4 to 8 carbons attached to Ar_3 ,

X is an alkyl group comprising 2 to 5 carbon atoms linking Ar_3 and Ar_4 ,

Ar_4 is a piperazine attached to X by a first nitrogen atom of Ar_4 , and

Q is a benzene ring optionally substituted with a biocompatible halogen and attached to Ar_4 at a second nitrogen atom of Ar_4 , and
wherein said vehicle is a slow release delivery vehicle.

83. (New) The composition of claim 82, wherein the slow release delivery vehicle is selected from the group consisting of a liposome, a microcapsule, and a polymer stabilized crystal.

500 / CHAPTER 30

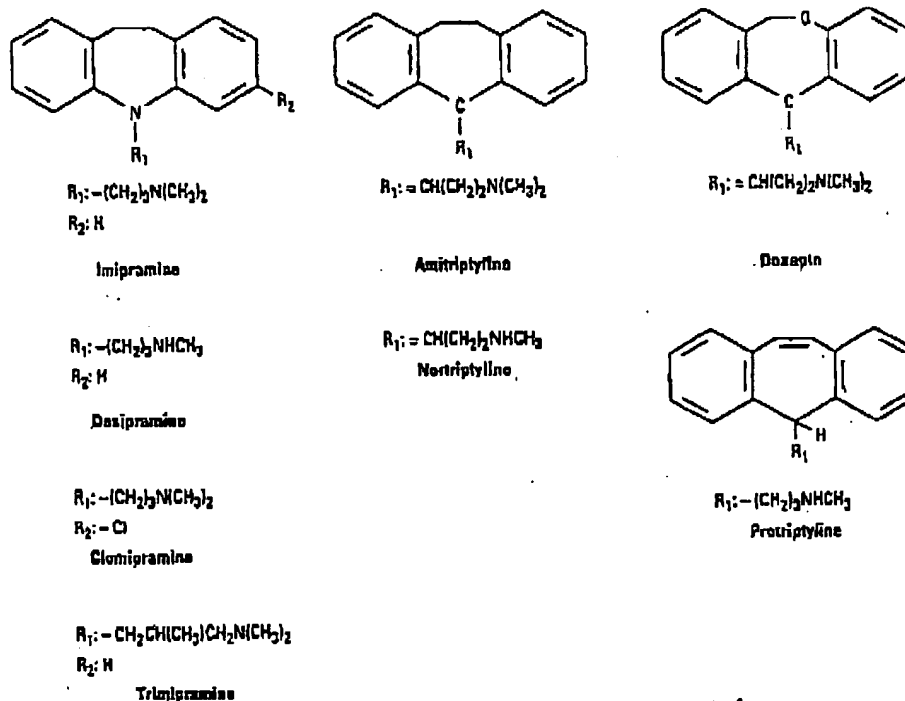


Figure 30-1. Structural relationships between various tricyclic antidepressants (TCAs).

tend to be very large. Tricyclics are metabolized by two major routes: transformation of the tricyclic nucleus and alteration of the aliphatic side chain. The former route involves ring hydroxylation and conju-

gation to form glucuronides; the latter, primarily demethylation of the nitrogen. Monodemethylation of tertiary amines leads to active metabolites such as desipramine and nortriptyline (which are themselves

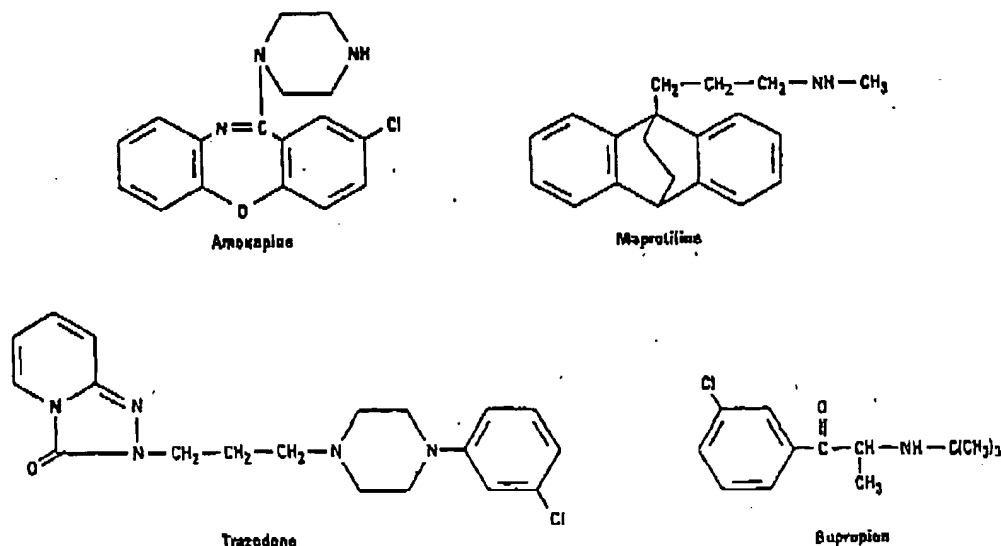


Figure 30-2. Second-generation antidepressants.

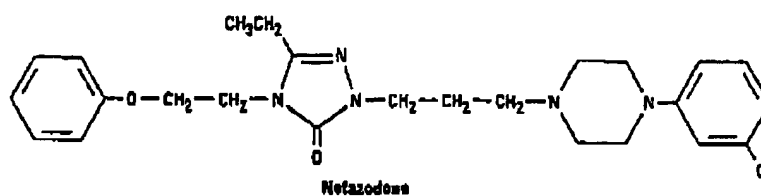
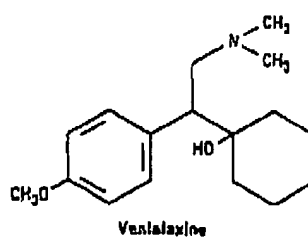
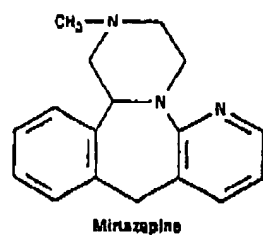


Figure 30-3. Third-generation antidepressants.

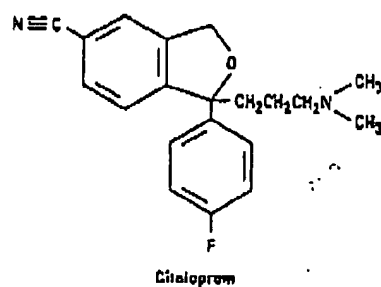
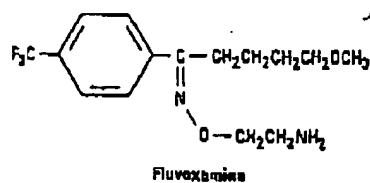
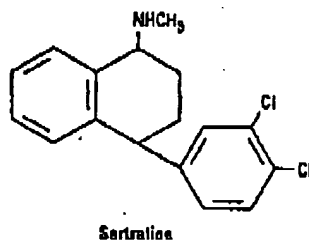
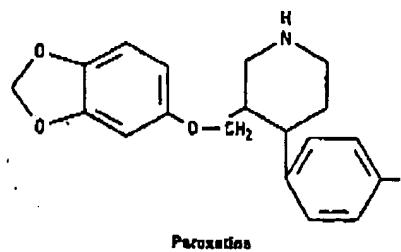
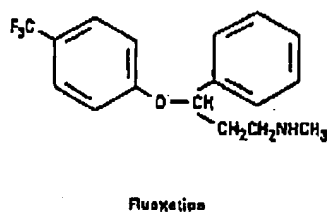


Figure 30-4. Selective serotonin reuptake inhibitors (SSRIs).

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